REMARKS

Claims 1 and 41-99 are pending in this application. Claims 73-75 are withdrawn from consideration. Claims 1 and 66 have been amended to recite that the temperature of the emulsion is lower than the boiling temperature of the organic solvent. Support for the amendments can be found throughout the specification, particularly at page 18, line 34 to page 19, line 4 of the instant PCT publication, WO 04/069284. Therefore, no new matter has been added.

Information Disclosure Statements

Applicant acknowledges Examiner's review of the Information Disclosure Statement (IDS) filed on 8/2/05 and the Supplemental Information Disclosure Statement filed on 11/18/05.

Regarding the IDS filed on 8/2/05, Applicant has attached a copy of the *identical* IDS, this time providing copies of the cited foreign references. Applicant apologizes for the oversight in failing to provide copies of the cited foreign references.

Applicant is grateful for the Examiner's consideration of the references cited in the IDS filed on 11/18/05.

Regarding the Supplemental IDS filed on **8/27/07** – it does not appear that the Examiner considered this IDS or the references cited therein.. The instant Office Action did not attach a copy of the references cited on the Form PTO/SB/08A, nor indicate that the IDS and its cited references were reviewed and considered. To ensure the references cited in the 8/27/07 Supplemental IDS will be considered, Applicant has attached a copy of the *identical* Supplemental IDS along with hard copies of the references.

Election/Restrictions/Rejoinder

Applicant acknowledges the Examiner's statement that the election of Group I was made *without traverse*. Applicant asserts the reply filed on 3/31/09 did in fact distinctly and specifically point out the supposed errors in the restriction requirement. Regardless, Applicant accepts Examiner's acknowledgement of the election of Group I and the following species: perfluorobutane as gas and DPPS as phospholipid.

In the reply filed on 3/31/09, Applicant requested rejoinder of claims 70-72, which were amended to depend on claim 66. While the Examiner did not address this request directly, claims 70-72 are stated to be under examination. Thus, it appears that Applicant's request for rejoinder has been granted.

Double Patenting Rejection

Claims 1, 41-73 and 76-99 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting over claims 38-42 of copending Application No. 10/584,382.

Claims 1, 41-73 and 76-99 were further provisionally rejected on the grounds of nonstatutory obviousness-type double patenting over claims 1-35 of copending Applicaiotn No. 11/641,289.

Claims 1, 41-73 and 76-99 were further provisionally rejected on the grounds of nonstatutory obviousness-type double patenting over claims 1-35 of copending Applicaiotn No. 11/660,188.

Applicants request that these provisional double patenting rejections be held in abeyance until otherwise allowable subject matter has been reached.

Rejections Under 35 U.S.C. § 103

Claims 1, 41-73 and 76-99 were rejected under 35 U.S.C. 103(a) as being unpatentable over Dugstad *et al.* (US 6,221,337) ("Dugstad"). The examiner admits that Dugstad does not teach use of an organic solvent in the preparation of an emulsion, but asserts that Dugstad's disclosure of perfluoropentane is within the scope of the invention. Applicants respectfully disagree.

Dugstad discloses (see in particular col. 8, lines 45 to col. 9, line 17) a process for preparing gas-filled microvesicles, where step (i) includes generating a dispersion of gas microbubbles by "*subjecting the lipid containing aqueous medium to any appropriate emulsion-generating technique [...] in the presence **of the selected gas***" (emphasis added, see col. 8, lines 51-66). As the Examiner admits (Office Action, p. 9) perfluoropentane is a disclosed gas. Indeed, the disclosure of Dugstad, in view of the specification as a whole, is clearly directed to **gaseous** perfluoropentane.

In contrast, the instant claims require an organic solvent in the **liquid** state. Moreover, as explained in the instant specification (see e.g. p. 26, lines 1-7 and Examples of WO 04/069284) use of an organic solvent in the liquid state to prepare an aqueous-organic emulsion comprising a phospholipid is a key step in the instantly claimed method as the mean size and size distribution of the microdroplets of solvent in the emulsion of step (a) determine in particular the mean size and size distribution of the gas microbubbles in the final reconstituted aqueous suspension.

As Dugstad fails to disclose or suggest emulsifying a lipid containing aqueous medium with **an organic solvent in the liquid state** , it cannot render claims 1 or 66 obvious. Applicant notes that in view of the failure of Dugstad to disclose a critical element of independent claims 1 and 66, this reference fails to render unpatentable the dependent claims for at least this reason. Thus Applicant submits that each of the claims is patentable over Dugstad.

Claims 1, 41-73 and 76-99 were rejected under 35 U.S.C. 103(a) as being unpatentable over Unger (WO 98/42384).[1] The Examiner asserts that Examples 9 and 10 of Unger differ from the claims in that a lyoprotective agent is not included and Unger does not specifically recite that sonication of perfluorohexane or bromoperfluorobutane results in an organic aqueous emulsion, but that allegedly this would have been obvious.

Applicants respectfully disagree. The cited Unger examples differ from the present invention by much more than the features pointed out by the examiner: Unger fails to teach or suggest lyophilization of a lipid-containing aqueous-organic emulsion.

Example 9 does not contain any lyophilization step, as required by the claimed method. The final product obtained following the procedure disclosed in Example 9 is in fact an aqueous-organic mixture containing lipid particles. There is no motivation for the skilled person to add an additional lyophilization step, as this mixture is in fact the final desired product to be used in the method disclosed by Unger (according to e.g. page 13, lines 6-24 of Unger).

Example 10 states that the procedure of Example 9 is followed except that (i) 1-bromoperfluorobutane is used in place of the perfluorohexane of Example 9 and added before the heating and sonication step (whereas in Example 9 perfluorohexane is added after heating); (ii) the lipid aggregates are lyophilized; and (iii) the aggregates are stored under air or insoluble gas.

As an initial matter, it should be noted that Example 10 is a prophetic example and that the accuracy in the drafting of the prophetic examples in the Unger reference is rather poor; for instance, in examples 8 and 16, perfluorohexane is twice erroneously mentioned (see page 64, line 32 and page 68, line 10) in place of the actual gas employed in these examples, i.e. 1-bromoperfluorobutane.

More importantly, by following the teaching of prophetic Example 10, the skilled person would not arrive at lyophilizing a lipid-containing aqueous-organic emulsion. As a matter of fact, 1-bromoperfluorobutane has **a boiling point of 43°C**, as indicated in table 1 on page 8, line 7 of WO 97/40679 (a patent application of the same applicant, copy of front page and page 8 here enclosed). As mentioned before, 1-bromoperfluorobutane is however added to the lipid mixture before the heating and sonication step (see in particular page 65, line 30); according to Example 9 (page 65, lines 16-17), the mixture is **heated to 45°C-50°C for one hour**. It is thus apparent that this heating treatment would inevitably result in the evaporation of the added 1-bromoperfluorobutane, having a boiling point lower than the temperature of the heated mixture. The result is that the subsequent lyophilization step foreseen

[1] Applicant notes that the Office Action cites "Unger (WO 98/04074)", but that this appears to be a typographical error. The correct citation appears to be Unger WO 98/42384 and this is the reference Applicant will address.

by prophetic example 10 is performed on an aqueous suspension of the lipids and not on an aqueous/organic emulsion of the lipids, as required instead by the present invention.

As explained above, use of an aqueous/organic emulsion of the lipids is a key step in the claimed method and provides advantages to the ultimate product. As Unger fails to teach or suggest this step or its advantages, it cannot render claims 1 or 66 unpatentable.

Applicant notes that in view of the failure of Unger to disclose a critical element of independent claims 1 and 66, this reference fails to render unpatentable the dependent claims for at least this reason.

Applicants respectfully maintain that claims 1, 41-73 and 76-99 are in condition for allowance, and request the issuance of a notice of allowance with respect to the same.

No fee is believed to be due with the filing of this Amendment and Response to Office Action. However, if any additional fee is necessary, applicant hereby authorizes such fee to be charged to Deposit Account No. 50-2168. If an interview with the Examiner would expedite the prosecution of this application, the Examiner is respectfully invited to contact the undersigned.

Favorable action is respectfully requested.

Respectfully submitted,

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